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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/600,659 | 07/20/2000 | Tommy Abrahamsson | 1103326 0629 | 9094 |

7590 02/09/2004

White & Case
Patent Department
1155 Avenue of the Americas
New York, NY 10036-2787

| EXAMINER | |
|---|---|
| LUKTON, DAVID | |
| **ART UNIT** | **PAPER NUMBER** |
| 1653 | |

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/600,659 | ABRAHAMSSON ET AL. | |
| | Examiner | Art Unit | |
| | David Lukton | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2-9,11-17,19-23,25,26,28-33,41,42,47,54 and 61* is/are pending in the application.

4a) Of the above claim(s) *3,9,11-17,19-23,25,26,28-33,47,54 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,5,8,41 and 42* is/are rejected.

7)☒ Claim(s) *6 and 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/15/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed (12/15/03), claims 9, 16, 19, 25, 28, 32 have been amended, and claims 10, 18, 27, 43-46, 48-53, 55-60, 62, 63 have been cancelled.

Claims 2-9, 11-17, 19-23, 25, 26, 28-33, 41, 42, 47, 54, 61 are pending, of which claims 3, 9, 11-17, 19-23, 25, 26, 28-33, 47, 54, 61 remain withdrawn from consideration. Claims 2, 4-8, 41, 42 are examined in this Office action. Claims 6 and 7 are objected to because of their dependence on rejected claims.

Applicants' arguments filed 12/15/03) have been considered and found persuasive in part.

The following §103 rejections are withdrawn:

- The rejection of claims 2, 4, 5, 8, 41, 42 as unpatentable over Ondetti ('277) in view of Grainger is withdrawn;

- The rejection of claims 2, 4, 5, 8, 41, 42 as unpatentable over Ondetti ('277) in view of Franson is withdrawn;

- The rejection of claims 2, 4-8, 41, 42 over Ondetti (*Biochem* **18**, 1427, 1979) in view of Bajzar (USP 5,993,815) further in view of Bylund (USP 5,955,433) or Antonsson (WO 94/29336) or Lofroth (WO 96/16671) is withdrawn;

- The rejection of claims 2, 4, 5, 8, 41, 42 Ondetti ('277) in view of Bajzar (*J Biol Chem* **271** 16603, 1996) or Boffa (*J Biol Chem* 273 2127, 1998) is withdrawn;

- The rejection of claims 2, 4-8, 41, 42 over Ondetti (USP 4,177,277) in view of Bylund (USP 5,955,433) or Lofroth (WO 96/16671) or Antonsson (WO 94/29336) is withdrawn;

- The rejection of claims 2, 4-8, 41, 42 are rejected under 35 U.S.C. §103 as being unpatentable over Eisenbach-Schwartz (USP 6,126,939) in view of Antonsson (WO 94/29336);

- The rejection of claims 2, 4, 5, 8, 41, 42 as unpatentable over Eisenbach-Schwartz (USP 6,126,939) in view of Grainger is withdrawn.

As indicated previously, the abbreviation "CPU" hereinbelow refers to carboxypeptidase U.

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 2, 4, 5, 8, 41, 42 are rejected under 35 U.S.C. §103 as being unpatentable over Eisenbach-Schwartz (USP 6,126,939) in view of Watson (USP 6,326,386)

As indicated previously, Eisenbach-Schwartz discloses (col 3, line 37) that the dipeptide Arg-Cys can be used to treat various inflammatory disorders, such as those recited in cols 5-6

of the reference. This compound is encompassed by formula I of claim 2 when the substituent variables correspond as follows:

R1-X = $C_4$-alkyl substituted with two basic groups
Y = $-CH_2-$
R2 = hydrogen
R3 = -COOH
R4 = -SH

The reference does not disclose that this dipeptide is an inhibitor of CPU, but this property is inherent. Eisenbach-Schwartz does not suggest combining this dipeptide with a thrombin inhibitor.

Watson discloses that thrombin inhibitors are effective to treat various inflammatory conditions. Also suggested (col 11, line 46) is that the disclosed thrombin inhibitors can be combined with other non-steroidal antiinflammatory agents.

Among the diseases disclosed by Watson to be successfully treated by thrombin inhibitors are myocardial infarction (col 1, line 53), Parkinson's Disease (col 11, line 3-4), Alzheimer's Disease (col 11, line 4) and arthritis (col 11, line 5). Eisenbach-Schwartz also teaches that these diseases can be successfully treated with the disclosed dipeptides. Relevant passages (of Eisenbach-Schwartz) are as follows: myocardial infarction (col 5, line 29-30), Parkinson's Disease (col 6, line 21), Alzheimer's Disease (col 6, lines 24-25), and arthritis (col 5, line 15). Thus, for the medical practitioner (of ordinary skill) endeavoring to treat myocardial infarction, Parkinson's Disease, Alzheimer's Disease or

arthritis, there would be motivation to combine the Eisenbach-Schwartz compound with one of the Watson compounds for additive effects. That is, in treating, e.g., myocardial infarction, a practitioner of the Eisenbach-Schwartz invention would recognize that a degree of efficacy can be achieved at a given dose of a drug, and that greater efficacy can be achieved by increasing the dose, or by combining the drug with another drug that exhibits the same therapeutic efficacy. Thus, the practitioner of the Eisenbach-Schwartz invention would have expected that by combining the Eisenbach-Schwartz peptide with a compound of Watson, he can achieve greater therapeutic efficacy than would be the case with just the Eisenbach-Schwartz peptide (for a given dosage).

The response filed 12/15/03 argues not that the Eisenbach-Schwartz peptide will fail to inhibit CPU, but that "it is not seen what [the peptide] has to do with... inhibition of CPU". The response also argues that Eisenbach-Schwartz does not inherently teach the claimed invention. However, the examiner has never argued that Eisenbach-Schwartz inherently teaches the claimed invention. Rather, what the examiner has argued is that the property of being a CPU inhibitor is inherent in the dipeptide Arg-Cys. By the same token, at least one compound falling within the scope of formula I (instant claim 2) is an inhibitor of macrophage migration. The fact that a compound is an inhibitor of macrophage migration does not mean that it cannot also be an inhibitor of an enzyme. It is not at all unusual for a single compound to exhibit multiple pharmacological effects. The instant specification asserts that if a compound falls

within the scope of formula I (claim 2), it is an inhibitor of CPU. Further, there is no evidence or assertion of record that the dipeptide Arg-Cys, which falls within the scope of formula I, is not an inhibitor of CPU. All of the evidence points to Arg-Cys being an inhibitor of CPU, and none suggests that it is not. Further, in order for this ground of rejection to be valid, it is not necessary that the "artisan of ordinary skill" have an opinion one way or another as to the propensity of Arg-Cys to inhibit CPU. It is sufficient that (a) this compound falls within the scope of formula I (claim 2) and (b) that there is motivation to combine this compound with a thrombin inhibitor. As is evident, both of these conditions are met.

The response also argues (in effect) that the mechanism of action of Arg-Cys when in the hands of the "artisan of ordinary skill" is far removed from the mechanism of action Arg-Cys when in the hands of a practitioner of the claimed invention. However, there is no evidence that the claimed compounds will not inhibit macrophage migration or T-cell adherence (to fibronectin). According to Eisenbach-Schwartz, at least one of the compounds falling within instant claim 2 will exhibit these properties; at the same time, there is no evidence that they will not. Thus, the dipeptide of Eisenbach-Schwartz is a CPU inhibitor, and at the same time, inhibits macrophage migration. The response also argues that Eisenbach-Schwartz has "nothing to do with... treatment of conditions that might respond to CPU inhibition". However, this is not true. On page 33 of the instant specification, it is asserted that various diseases

can be successfully treated with CPU inhibitors. Such diseases include, e.g., Alzheimer's, atherosclerosis and septic shock. In fact, the Eisenbach-Schwartz peptides can be used to treat the same diseases (see cols 5-6).

The response also argues that the specification provides evidence of a synergistic effect when a CPU inhibitor is combined with a thrombin inhibitor. Table I shows that when The CPU inhibitor MERGETPA is combined with the thrombin inhibitor inogatran, the amount of fibrin deposited in the lungs is less than would be the case for either inhibitor alone, and moreover is less than would be expected if merely an additive effect were occurring. A similar result is shown in each of tables II and III. The results do tend to suggest that when the thrombin inhibitor inogatran or melagatran is combined with a CPU inhibitor falling within the scope of formula I (claim 2), "unexpected results" are obtained. The issue, however, is the extent to which the "unexpected results" may extend to other thrombin inhibitors which were never contemplated by applicants, or at least which were never disclosed in the specification. Other thrombin inhibitors may exhibit different pharmacokinetics/ biodistribution than may be exhibited by inogatran or melagatran. Or the mechanism of thrombin inhibition may be different. In addition, the claims do not actually require that thrombin inhibition ever occur at all. Further, if the artisan of ordinary skill is intent on treating Alzheimer's Disease or atherosclerosis or septic shock (for example), he is unlikely to be concerned about the degree of inhibition of fibrin deposition in the lungs. Thus, for treatment of a

disease in which fibrin deposition in the lung does not occur, the results presented (tables I – III, specification) are not especially "unexpected".

The rejection is maintained.

*

Claims 2, 4, 5, 8, 41, 42 are rejected under 35 U.S.C. §103 as being unpatentable over Ondetti (USP 4,177,277) in view of Watson (USP 6,326,386).

Ondetti discloses (col 3, line 18+) compounds that are useful to treat cardiovascular conditions and inflammatory conditions. The compounds can also be used (col 7, line 57) to treat oedema. For example, the following compound is encompassed by instant claim 2 as well as the prior art genus (applicants' variables are used hereinbelow):

R1-X = aminopropyl
Y = $-CH_2-$
R2 = hydrogen
R3 = -COOH
R4 = -SH

Ondetti does not suggest combining the disclosed compounds with thrombin inhibitors.

Watson discloses (col 1, line 50+; col 10, line 62) that thrombin inhibitors can be used to treat various cardiovascular conditions. Also disclosed (col 1, line 55) is treatment of inflammation and (col 1, line 55 and col 10, line 65) treatment of oedema. Watson does not suggest combining the thrombin inhibitors with the compounds of Ondetti. However, the artisan of ordinary skill would have been motivated to combine the compounds of

Ondetti with the compounds of Watson for additive effects. This would be true whether the "artisan" were endeavoring to treat cardiovascular disease, or inflammation or oedema. The artisan of ordinary skill would have expected that, for a given dose of the Ondetti compound, addition of a thrombin inhibitor would provide further therapeutic benefit. The claims are thus rendered obvious on this basis alone. In addition, Watson suggests (col 11, line 46) that thrombin inhibitors can be combined with other non-steroidal antiinflammatory agents. This suggestion provides further impetus to combine thrombin inhibitors with non-steroidal antiinflammatory agents such as those disclosed by Ondetti.

The response filed 12/15/03 argues that plasma carboxypeptidase B (a.k.a "carboxypeptidase U") is not the same as pancreatic carboxypeptidase B. In support of this assertion, the response points to the following two references: Skidgel ("Zinc Metalloprotases...", 1996) and Bouma (*Thrombosis Res.* 101, 329, 2001). These references do convey that there are slight differences between the pancreatic and plasma carboxypeptidases. In particular, the plasma enzyme contains 309 amino acids, and the pancreatic enzyme contains 306. However, the claims are not drawn to an enzyme *per se*; the claims do not even require that an enzyme be inhibited. In fact, if the claimed formulation were simply placed in a vial, no inhibition of any enzyme would occur. Thus, the claims do not require that plasma carboxypeptidase ever be inhibited. What matters is that the second of the two compounds present (in the claimed

formulation) have the property of being a plasma carboxypeptidase inhibitor. It may be the case that Ondetti discloses only inhibition of the pancreatic enzyme, not the plasma enzyme. But the fact that a given compound has the property of inhibiting one enzyme does not mean that it cannot inhibit another. The reality of this, in fact, is conveyed in the two references cited in the response (filed 12/15/03). For example, the compounds MGTA and GEMSA inhibit both the pancreatic and the plasma enzyme, as do cadmium ions and various chelators. Thus, the fact that the Ondetti compounds inhibit the pancreatic enzyme does not mean that they do not also inhibit the plasma enzyme. Given that the Ondetti compounds fall within the scope of formula I (claim 2), they are inhibitors of the plasma enzyme (a.k.a. "CPU"). No evidence has been presented, either at the time of filing or subsequent thereto that compounds falling within the scope of formula I are not CPU inhibitors. In fact, there has been no assertion in this response (or the previous response) that the compounds of formula I are not CPU inhibitors. A compound and its properties are inseparable; a compound cannot have one inherent property when in the hands of applicants, and another inherent property when in the hands of the "artisan of ordinary skill". Thus, the compounds of Ondetti are inhibitors of both the plasma carboxypeptidase and the pancreatic carboxypeptidase. The only other issue is that of motivation to combine one of the carboxypeptidase inhibitors of Ondetti with a thrombin inhibitor. As indicated above, such motivation is present, and the existence of (adequate) motivation does not require

the artisan of ordinary skill to have an opinion as to whether the (Ondetti) compounds will inhibit both the plasma and the pancreatic enzyme, or just the pancreatic enzyme.

The response also argues that the specification provides evidence of a synergistic effect when a CPU inhibitor is combined with a thrombin inhibitor. Table I shows that when the CPU inhibitor "MERGETPA" is combined with the thrombin inhibitor inogatran, the amount of fibrin deposited in the lungs is less than would be the case for either inhibitor alone, and moreover is less than would be expected if merely an additive effect were occurring. A similar result is shown in each of tables II and III. The results do tend to suggest that when the thrombin inhibitor inogatran or melagatran is combined with a CPU inhibitor falling within the scope of formula I (claim 2), "unexpected results" are obtained. The issue, however, is the extent to which the "unexpected results" may extend to other thrombin inhibitors which were never contemplated by applicants, or at least which were never disclosed in the specification. Other thrombin inhibitors may exhibit different pharmacokinetics/ biodistribution than what may be exhibited by inogatran or melagatran. Or the mechanism of thrombin inhibition may be different. In addition, the claims do not actually require that thrombin inhibition ever occur at all. Further, if the artisan of ordinary skill is intent on treating cardiovascular disease, or inflammation or oedema, he is unlikely to be concerned about the degree of inhibition of fibrin deposition in the lungs. Thus, for treatment of a disease in which fibrin deposition in the lung does not occur, the results presented (tables

I – III, specification) are not especially "unexpected".

The rejection is maintained.

*

Claims 2, 4, 5, 8, 41, 42 are rejected under 35 U.S.C. '103 as being unpatentable over Eisenbach-Schwartz (USP 6,126,939) in view of Franson (USP 6,020,510).

As indicated previously, Eisenbach-Schwartz discloses (col 3, line 37) that the dipeptide Arg-Cys can be used to treat various inflammatory disorders, such as those recited in cols 5-6 of the reference. This compound is encompassed by formula I of claim 2 when the substituent variables correspond as follows:

R1-X = $C_4$-alkyl substituted with two basic groups
Y = $-CH_2-$
R2 = hydrogen
R3 = -COOH
R4 = -SH

The reference does not disclose that this dipeptide is an inhibitor of CPU, but this property is inherent. Eisenbach-Schwartz does not suggest combining this dipeptide with a thrombin inhibitor.

Franson discloses (col 7, line 58+) compounds that inhibit thrombin-induced platelet aggregation, and at the same time, can be used to treat various inflammatory conditions. Many of the disorders that can be treated with the Franson compounds are the same as those which can be treated with the Eisenbach-Schwartz peptides. For example, myocardial

infarction can be treated with both the Franson and the Eisenbach-Schwartz compounds (see Eisenbach-Schwartz col 5, line 29-30 and Franson col 7, line 52).

For the reasons given above (the §103 rejection over Eisenbach-Schwartz in view of Watson), the claims are rendered obvious.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

*

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton 2/2/04

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